DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

HFI-35 m3360/n

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (949) 798-7600

WARNING LETTER

DEC 3 0 1999

CERTIFIED MAIL – RETURN RECEIPT REQUESTED

Julio C. Liberal
President
Universal Packaging Systems, Inc.
4575 Danito Court
Chino, CA 91710

W/L 20-00

Dear Mr. Liberal:

During an inspection of your manufacturing facility located at 4575 Danito Court, Chino, CA, concluded October 4th, 1999, an FDA investigator documented deviations from the Current Good Manufacturing Practices (cGMPs) for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, (CFR) §211). Those deviations cause all drug products manufactured at your facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The violations from 21 CFR §211 include:

1. Failure to reject any lot of components that does not meet appropriate specifications of identity, strength, quality and purity [§211.84(e)]. De-ionized water that failed microbiological specifications was used in the manufacture of at least two OTC drug product batches (lot numbers 32957 and lot number 32676-1).

2. Failure to follow a testing program designed to assess the stability characteristics of drug products [§211.166(a)]. For example, you are not conducting stability tests at the intervals required in your written stability test procedure, nor do you adequately control the storage of stability samples.

3. Failure to maintain complete records of all stability testing performed in accordance with §211.166, Stability Testing [§211.194(e)]. For example, there are no records documenting temperature monitoring of the stability room where OTC drug product stability samples are stored.

4. Failure to maintain equipment to prevent malfunctions or contamination that would alter the safety, identity, strength and purity of the drug product [§211.67(a)]. For example, you have no validation that your cleaning and sanitation procedures prevent significant cross contamination from multi-use manufacturing process equipment.

5. Failure to maintain and follow written procedures that describe the receipt, identification, storage, handling, sampling examination and/or testing of labeling [§211.122(a)].

6. Failure to destroy outdated labels [§211.122(e)]. For example, labels for outdated products were observed in the label storage area.

7. Failure to construct equipment so that surfaces that contact components are not reactive, additive or absorptive so as to alter the safety, identity, strength, quality and purity [§211.65(a)]. For example, the de-ionized water system has leaks at several locations including a drug manufacturing area.

8. Failure to maintain records documenting the maintenance of equipment to prevent malfunction that would alter the safety, identity, strength, quality and purity of the drug product [§211.67(c)]. For example, there are no records documenting the temperature monitoring of raw material storage refrigerators and laboratory media storage refrigerators.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your Chino, CA facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, New Drug Applications, Abbreviated New Drug Applications or export approval requests may not be approved until the above violations are corrected.

We acknowledge the receipt of your response to the Form FDA-483 issued at the conclusion of the inspection at your facility. However, your firm's inability to make or implement previously promised corrections verified during this inspection brings into question your firm's commitment to voluntarily comply with the applicable federal laws and regulations, including current Good Manufacturing Practices. You should be aware that we consider several of the FDA-483 observations (lack of investigation into Out of Specification results, lack of validation for cleaning and/or sanitization procedures and lack of label control and label control procedures) to be highly significant. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

In addition, we offer the following comments:

We are concerned that no investigation was conducted after de-ionized water failed microbiological specifications. This water was used in the production of at least two OTC drug product batches (lot numbers 32957 and 32676-1). 21 CFR §211.192 requires an investigation if any component used in the manufacture of drug products fails to meet specifications. Investigating is the only way to determine the actual cause of the failure and develop a sound corrective action to ensure the failure does not recur.

Our investigator observed that raw data from laboratory testing is being recorded on form [redacted] Certificate of Analysis instead of in bound, laboratory notebooks. In your response to the Form FDA-483 observation, you say that because you are following documented procedures, record

notebooks are not required. While we agree that you do not need bound notebooks, any record where raw data is recorded needs to be controlled so that you, as responsible head, know that all tests performed are being reported. Uncontrolled work sheets can lead to the discarding of information in violation of §211.194. In addition, §211.194 requires information be kept that is not recorded on form [redacted], Certificate of Analysis.

Additionally, our investigator documented instances of product that did not pass specifications being shipped from your facility to the "owner" of the drug product. We understand that, as a contract manufacturer, you manufacture products for distributors, labelers and others under contract and may not "own" the product. However, 21 CFR §210.3(b)(15) defines the quality control unit as any person or organizational element designated by the firm to be responsible for the duties relating to quality control. 21 CFR §211.22 describes the function of the quality control unit, which includes, among other things, the authority to approve or reject all drug products. If you do not have final release authority for products you manufacture, it is your obligation to inform the person or organization with that authority that the product you manufactured failed specifications. This would include failing results obtained after the product is released and/or distributed as required in §211.192.

You should notify this office in writing within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which corrections will be completed.

Your written response should be directed to the Food and Drug Administration, Attention:

Director, Compliance Branch
Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Sincerely,

Thomas L. Sawyer
Acting District Director

cc: California Department of Health Services, Food & Drug Branch
601 N. 7th Street
Sacramento, California 94234-7320
Attn: Stuart Richardson, Jr., Chief